

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

DATE: January 16, 1978

TO : Donald Fredrickson

FROM : Maxine Singer

SUBJECT: Section I of Proposed Revised Guidelines; Definition and Problem of List of "Not Novel"

1. These comments start from the wording proposed by Paul Berg (attached to his letter to Don Fredrickson, dated December 5, 1977).

2. Regarding the definition I believe we must recognize that no scheme will be perfect. Unanticipated experimental proposals will eventually illuminate ambiguities and difficulties in the definition, regardless of how good the scheme seems at the beginning. As pointed out before, it is urgent that we remove those experiments widely agreed to be of no possible hazard from coverage by the Guidelines. The expense in time, money, and frustration engendered by bureaucratic requirements that are irrelevant to safety (or anything else) should be avoided for all the self-evident reasons but also because they stimulate disrespect for the important aspects of the Guidelines.

3. For all the reasons we have discussed before I propose leaving the first two sentences as they are.

4. In sentence 3: the problem is "normal physiological processes". But it is important to recognize that the ambiguity will be useful as well as troublesome. It will be Don Fredrickson who will decide, with advice of ORDA and RAC what is "normal". And our notions of what is "normal" are likely to evolve.

5. I propose moving the final sentence (now #5) to become sentence #4. This is a general statement that "self" experiments are excluded. Bill Gartland believes the present wording makes it clear that "self" experiments do not even need to appear on a list to be excluded. I believe the wording is ambiguous in that regard but I do think such experiments should be excluded. I suggest, therefore, the following wording for new sentence #4:

"Thus, recombinant DNA molecules are not considered novel and are, therefore, not covered by these Guidelines, when all DNA components are derived from genomes known to replicate within the organism or cell used to propagate the recombinant DNA."

6. It may be desirable to add, parenthetically or in a footnote, the following clarification:

"This does not include DNA components present in such genomes only as a result of prior recombinant DNA experiments."

7. Two more comments on this proposal.

a) Some might argue for a list here, or even a short list of examples. But I believe that to be unnecessary. The phrase "from genomes known to replicate within" is very specific. The proposed qualification is designed to respond to Bernie Talbot's reservation about the exclusion.

b) A decision will be needed regarding the inclusion of Footnote #1. My earlier comments made it clear that I believe the footnote unnecessary. Hopefully we will have more information on this after the virus meeting in London.

8. The final sentence should deal with those "non-self", "normal" exchangers that will need to be on a list. Our thinking about this would be helped if Bill Gartland could supply a list of those relevant cases he has already been asked about. But there is a lot to be said for a rather general statement, such as the following:

"In addition, the Director of the NIH, with the advice of the Recombinant DNA Molecule Advisory Committee, and upon request of investigators and submission of relevant data, may determine that other combinations of recombinant DNAs and host organisms are not novel and are, therefore, not covered by these Guidelines."

9. It will be very helpful if the beginnings of such a list could be attempted, in order to understand better the problems. Some of these should be relatively easy, others difficult. Bill Gartland's summary of existing requests could serve as a basis for discussion. I would add that I do not believe it is very fruitful to start the process by trying to determine some general definition of "normal physiological processes". Consideration of this question within the context of each case that comes up will be much easier and more efficient. For example, most people will probably agree that the recent Chang and Cohen experiments do not lead to the conclusion that the system mouse mitochondrial DNA--E. coli vector--E. coli should be on the list. But most people will readily agree that the system DNA from nonpathogenic Salmonella--E. coli vector--E. coli should be on the list.

10. To summarize, I propose the following wording for paragraph 1, part I.

// The purpose of these Guidelines is to establish procedures for constructing and handling organisms and viruses containing recombinant DNA molecules. Recombinant DNA molecules are defined as molecules which have been constructed outside of living cells by joining natural or synthetic

DNA segments to DNA molecules that can replicate or be integrated into the genome of a living cell. // However, the recommendations contained herein pertain only to organisms and viruses that contain "novel" recombinant DNAs where the word "novel" applies to molecules containing a) natural DNA segments or reverse transcripts from species not known to exchange DNA by normal physiological processes or b) synthetic DNA segments whose nucleotide sequence can or might be expressed as a polynucleotide or polypeptide that is not known to be made in the chosen host cells. *omit*

*is not known to pose no signif. risk to health
know not to be -*

Thus, recombinant DNA molecules are not considered novel and are, therefore, not covered by these Guidelines, when all DNA components are derived from genomes known to replicate within the organism or cell used to propagate the recombinant DNA.

In addition, the Director of the NIH, with the advice of the Recombinant DNA Molecule Advisory Committee, and upon request of investigators and submission of relevant data, may determine that other combinations of recombinant DNAs and host organisms are not novel and are, therefore, not covered by these Guidelines. //

11. Note that this wording (as all current proposals) requires adding a section to the Guidelines for exchangers that do not appear on the list.

12. As I indicated above, there are arguments for omitting the final sentence completely (see Bernie's memo).

P.S. I have now had the opportunity to look at Bill Gartland's material. It confirms my hunch that general definitions of "normal physiological processes will not be helpful". A few examples illustrate some of the problems in establishing a list. I think the question of pathogenicity will be the issue of concern. It may be that sentence 5 should be so qualified.

Some examples:

a. E. coli K12 host-vector with DNA of Klebsiella aerogenes.

E. coli and K. aerogenes are known to undergo intergeneric chromosome transfer. K. aerogenes was never classified as a pathogen by CDC since it was not classified as a Klebsiella at the time CDC lists were made. It was then classified as Aerobacter aerogenes (Class 1, CDC). This system might then be a candidate for the "list".

b. S. typhimurium host-vector with E. coli DNA or E. coli systems with S. typhimurium DNA might be on list - with specified S. typhimurium strains.

cc:

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